Division of Diabetes, Endocrinology and Metabolic Diseases

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RACE/ETHNIC DISPARITIES IN THE INCIDENCE OF DIABETES COMPLICATIONS (PA-02-096)

FY 2003 Action
This Program Announcement (PA) will replace PAS 00-028, which is expiring. The PA solicits research to understand racial/ethnic disparities in the development of microvascular and macrovascular complications of diabetes.

Background
Racial and ethnic groups differ considerably in the frequency of diabetes in their populations. For example, rates of type 2 diabetes are particularly high among American Indians, African Americans, Hispanic Americans, and Asian and Pacific Islanders. The microvascular complications of diabetes are a major problem in these groups, not only because their frequency of diabetes is high, but also because there is evidence that complications occur more frequently among individuals with diabetes in these minority populations. However, the reasons for these differences are not well understood.

The Diabetes Control and Complications Trial (DCCT), for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS), for type 2 diabetes, established the importance of intensive diabetes control in dramatically reducing the devastating complications that result from poorly controlled diabetes. In addition, numerous studies have demonstrated that intensive blood pressure control is essential in preventing both micro- and macrovascular complications of diabetes. Aggressive management of dyslipidemia has also been shown to decrease macrovascular complications. Some of the racial differences in diabetic complications may be explained by differences in availability and quality of health services. There may be differences by race/ethnicity and socioeconomic status in self-care practices, health care provider practices, and/or access to quality health care and prevention services that directly impinge on the frequency and magnitude of risk factors for complications and the intensity of medical care for early stages of complications to prevent progression to end-stage disease.

In addition to differences in blood glucose, lipid and blood pressure control, which may be modified by improved medical care, genetic susceptibility and other biological risk factors may contribute in unknown ways that lead to complications. This is suggested by the clustering of complications (especially nephropathy) within families and by the excess risk of retinopathy in Hispanics versus non-Hispanics that remains when the degree of hyperglycemic exposure is taken into account.

Finally, lifestyle, psychosocial factors, stress, family structure, social support, diet and culture, and socioeconomic status vary among racial and ethnic minorities and may contribute to differential risk of developing diabetes complications and progression of complications. Little is known about how these behavioral factors influence the risk of complications and the effectiveness of interventions designed to prevent or reduce diabetes complications in racial and ethnic minority groups.

In contrast to microvascular complications, racial and ethnic minorities with diabetes often have lower rates of macrovascular disease than Caucasian population groups. Angina, myocardial

infarction, and other forms of coronary heart disease appear to be less common in African Americans, Mexican Americans and Native Americans than in non-Hispanic whites. This difference is particularly striking given the higher incidence of diabetes in these populations. The factors that account for the differing macrovascular disease rates are unknown. For example, the relative contribution of glycemia (*versus* other risk factors) to cardiovascular risk in these minority populations has not been studied.

Research Goals and Scope

The overall objective of this Program Announcement is to understand racial/ethnic disparities in the development of the micro- and macrovascular complications of diabetes. It is recognized that both biologic and non-biologic factors may be operating in these populations. Approaches may include metabolic, genetic and/or epidemiologic studies in representative populations. Investigators are encouraged to incorporate appropriate surrogate markers for complications into study design to shorten the duration of studies. Such surrogate markers might include early indicators of end-stage complications (background retinopathy, albuminuria, serum creatinine, basement membrane thickening, EKG, and carotid ultrasound).

Appropriate topics for investigation would include but are not limited to: (1) epidemiologic studies to determine the rates of microvascular (nephropathy, retinopathy, and neuropathy) and macrovascular (cardiovascular disease and stroke) diabetic complications in appropriate representative samples of contemporary populations; (2) studies to identify genes which might affect the development and progression of micro- and macrovascular complications in different populations; (3) state-of-the-art, hypothesis-driven metabolic studies to determine whether there are differences in metabolism, insulin sensitivity, energy expenditure, beta cell function, and body composition that might influence glycemic control and risk of complications in different populations; (4) studies to compare the contribution of glycemia versus other risk factors (e.g., smoking, hyperlipidemia, body composition, blood pressure) in the development of micro- and macrovascular disease in patients with diabetes, and to study how treatment of these factors may influence rates of development of complications in different racial/ethnic groups; (5) studies to investigate environmental factors, such as medical care, behavior and lifestyle, and socioeconomic status, that may contribute to risk for development and progression of complications; and (6) studies to determine whether different pathophysiologic mechanisms or risk factors are operative among subgroups within racial/ethnic minorities (e.g., different subgroups of Hispanic Americans, such as Mexican Americans, Puerto Ricans, Caribbean Hispanics, Cuban Americans).

Understanding the basis for differing susceptibilities could provide information that would lead to specific therapies likely to be useful in various subpopulations at high risk for the development of diabetes complications.

INSULIN SIGNALING AND RECEPTOR CROSS-TALK (PAS-99-112)
http://grants.nih.gov/grants/guide/pa-files/PAS-99-112.html

FY 2003 Action
The purpose of this initiative is to stimulate novel and innovative research to investigate the fundamental underlying mechanism(s) of action of signaling through the insulin receptor and its cross-talk with other cellular receptors and signaling pathways. Of particular interest is how such signaling interactions may affect the development and/or progression of diabetes and its complications. This announcement was initially issued in FY 1999 and active through FY 2002.

Background
Diabetes mellitus is characterized by the inappropriate regulation of serum glucose levels. Both type 1 and type 2 diabetes are characterized by insulin deficiency, with type 2 diabetes also characterized by cellular resistance to insulin action. Insulin acts through a cell surface receptor and several downstream effectors to regulate cellular growth and metabolism. Insulin target tissues also respond to hormones, growth factors and cytokines that have the potential to modify insulin responses. Receptors for many of these modifying factors initiate signals that may overlap or modulate insulin-responsive biochemical pathways in cells. Thus, the changes in cell growth or metabolism that are associated with insulin action often reflect an integrated and coordinated response made in the context of a complex cellular microenvironment (cross-talk). While much progress has been made in defining the biochemistry of the insulin-response pathway and in documenting insulin-regulated changes in gene expression, significant gaps remain. For example, our understanding of how a cell's complex biochemical history may modify subsequent responses to insulin, and of how multiple environmental cues regulate insulin action in target tissues *in vivo*, remains rudimentary. Information generated *via* these and related studies of signaling cross-talk in insulin-responsive tissues have the potential to provide important clues to the mechanisms that underlie diabetes pathophysiology, and may have important implications for the design and implementation of new therapeutics to treat diabetes and its complications.

Research Goals and Scope
The specific objectives of this research solicitation include, but are not limited to: (1) determining the specificity of signaling through the insulin receptor, including delineation of metabolic versus mitogenic responses; (2) signaling through receptors for other soluble factors in insulin target tissues, including growth factors and cytokines, and potential modifying effects of these soluble factors on insulin action, diabetes pathophysiology and its complications; (3) signaling *via* cell-bound ligands in insulin-responsive tissues, including receptors and ligands regulating cell adhesion and interactions with endothelium and extracellular matrix, and the impact of these signals on insulin responses generated *in vitro* and *in vivo*; (4) genomic, proteomic, and other biochemical approaches to identify novel factors associated with insulin action in target tissues, including putative targets for therapeutic intervention; (5) structural biology of cell surface receptors and signal relay molecules that transduce or modify insulin actions, including enzymes, protein scaffolds, and higher-order complexes capable of integrating signals generated by receptor cross-talk in insulin-responsive cells; (6) factors regulating cell surface expression of functional insulin receptors, and other cell surface receptors, in diabetes and its complications; (7) interactions between and among transcription factors that mediate the

effects of insulin on gene expression: cross-talk with transcription factors responding to other signaling pathways; (8) signaling cross-talk between the insulin receptor and nuclear receptors, including effects on development and/or progression of diabetes and its complications; (9) identification of factors involved in cell signaling that may cause resistance to insulin action in insulin-sensitive cells (e.g., muscle, adipose) and novel approaches to overcoming or bypassing such resistance; and (10) the mechanism of action of non-peptide receptor analogs and their potential efficacy as therapeutic agents.

RACIAL AND ETHNIC DIFFERENCES IN THE ETIOLOGY OF TYPE 2 DIABETES IN MINORITY POPULATIONS (PA-02-117)
http://grants1.nih.gov/grants/guide/pa-files/PA-02-117.html

FY 2003 Action
This Program Announcement solicits research to enhance our understanding of the underlying metabolic and physiologic mechanisms that contribute to the racial and ethnic differences in the incidence and pathophysiology of type 2 diabetes in the U.S.

Background
It is well recognized that there are major differences in the prevalence of type 2 diabetes among race/ethnic groups in the U.S. Substantial progress has been made toward identifying population-based risk factors for the development of type 2 diabetes that might lead to these race/ethnic disparities. Such established risk factors include, for example, genetic predisposition, total and central obesity, duration of obesity, high caloric intake, and physical inactivity. Factors such as socioeconomic status, acculturation, and stress may also be important. Individuals who have progressed along the pathogenic course toward diabetes are at higher risk of developing overt disease, and these individuals include those with insulin resistance, impaired glucose tolerance, gestational diabetes, and reduced beta cell function.

Although these diabetes risk factors appear to operate in all race/ethnic groups, it is not known whether specific groups are inherently different in the ways they respond to risk factors, which may lead to their differential susceptibility to diabetes. Environmental, genetic, and metabolic differences may underlie the disparity in diabetes rates, and physiological outcomes of risk factors may arise from a complex interplay of genetic and non-genetic (behavioral, lifestyle, and environmental) factors.

Epidemiologic studies have documented the differing risk for diabetes among race/ethnic groups and have established the identity of diabetes risk factors. However, with few exceptions, these studies have not been designed to examine in depth the metabolic and physiologic effects of diabetes risk factors in specific race/ethnic populations. Consequently, there is an important need for carefully designed clinical studies to investigate these issues in representative samples of the various U.S. race/ethnic groups.

Research Goals and Scope
The overall objective of this Program Announcement is to determine the metabolic and physiologic reasons for disparities in the incidence of type 2 diabetes in minority race/ethnic populations. Such information could lead to new prevention and treatment strategies, especially for high risk groups. Additionally, information from these studies would be important for devising cost-effective approaches to phenotyping patients with type 2 diabetes and individuals at risk for developing diabetes. The ability to characterize and identify discrete subgroups of type 2 diabetes would be essential in genetic studies of this disease.

Studies to investigate the behavioral, socioeconomic, psychosocial, cultural, family, and community factors that influence the individual's risk for developing type 2 diabetes and how these factors can lead to racial and ethnic disparities in incidence rates are clearly of importance.

Understanding these issues is vital to the development of culturally appropriate prevention strategies to reduce risk across racial and ethnic groups. However, studies to investigate non-biologic factors should not be submitted under this Program Announcement, which will focus on biologic factors responsible for race/ethnic disparities in the incidence of type 2 diabetes.

Appropriate topics for investigation might include state-of-the-art, hypothesis-driven metabolic studies in representative samples of U.S. race/ethnic groups; the temporal relationship of changes in body weight and body composition, glucose tolerance, and insulin resistance; beta cell function studies, such as beta cell assessments with longitudinal follow up, beta cell responses to fatty acids, hyperglycemia, amino acids, and insulin resistance; clinical studies of fat metabolism and insulin resistance; temporal relationships among the components of Syndrome X; and the role of the *in utero* environment on the subsequent development of impaired glucose tolerance or type 2 diabetes.

TRANSLATIONAL RESEARCH FOR THE PREVENTION AND CONTROL OF DIABETES (PA-02-153)
http://grants1.nih.gov/grants/guide/pa-files/PA-02-153.html

FY 2003 Action
This Program Announcement (PA) replaces PA 01-069, which is being updated to reflect the results of the Diabetes Prevention Program (DPP). This initiative solicits research to translate recent advances in the prevention and treatment of type 1 or type 2 diabetes into clinical practice for individuals and communities at risk. It seeks applications for clinical and behavioral studies to develop and test (1) improved methods of health care delivery to patients with or at risk of diabetes; (2) improved methods of diabetes self management; and (3) cost effective community-based strategies to promote healthy lifestyles that will reduce the risk of diabetes and obesity. Studies should focus on testing strategies for achieving objectives that have already been proven beneficial, such as (1) control of glycemia and other risk factors for diabetic complications, including hypertension and dyslipidemia; and (2) altering life style to prevent or delay the onset of type 2 diabetes in at risk populations, including children and adolescents. Of particular interest are interventions that focus on underserved and minority populations.

Background
Several large, controlled clinical trials have established "gold standard" approaches for treating type 1 and type 2 diabetes, and for preventing type 2 diabetes in individuals at high risk for developing the disorder. Programs are needed to translate the results of these trials into widespread clinical practice. Translational research related to obesity, a major risk factor for type 2 diabetes, is also needed.

The Diabetes Control and Complications Trial (DCCT), for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS), for type 2 diabetes, established the importance of intensive diabetes control in dramatically reducing the devastating complications that result from poorly controlled diabetes. Both the DCCT and the UKPDS demonstrated the efficacy of intensive glucose control in reducing the risk for the microvascular complications of diabetes. In addition, results from the UKPDS and other trials demonstrate that cardiovascular events are reduced in patients with type 2 diabetes through rigorous control of blood pressure and LDL-cholesterol.

Unfortunately, the advances of these studies have not been successfully incorporated into general health care practice. Prevention and treatment of long-term micro- and macrovascular complications remain a critical problem in the management of type 1 and type 2 diabetes mellitus. In the U.S., diabetes is the leading cause of new blindness in working-age adults, of new cases of end stage renal disease and of non-traumatic lower leg amputations. In addition, cardiovascular complications are now the leading cause of diabetes-related morbidity and mortality, particularly among women and the elderly. In adult patients with diabetes, the risk of cardiovascular disease is two- to four-fold greater than in nondiabetics. For cardiovascular disease, comorbid conditions (hypertension, dyslipidemia and hyperinsulinemia) combine with hyperglycemia to contribute to accelerated atherosclerosis. These additional risk factors may also contribute the microvascular disease. Thus, control of hyperglycemia, although critical, is not sufficient to substantially reduce morbidity and mortality. Available data demonstrate that

patients with diabetes would benefit from more aggressive and comprehensive risk factor management.

Underutilization of current knowledge was highlighted in recent studies of diabetic individuals that demonstrated a low frequency of achievement of targets for management of glycemia, blood pressure, and lipids, aspirin use, self-monitoring of blood glucose, regular foot care, and ophthalmic examinations, all of which markedly reduce the incidence and progression of diabetic complications. Alarmingly, less than 2 percent of adults with diabetes receive the level of care that has been recommended by the American Diabetes Association. Thus, it is clear that effective mechanisms for diabetes treatment, shown by clinical trials to reduce the burden of diabetes, are not being implemented.

The difficulties inherent in achieving good glucose control and preventing diabetes complications make prevention a compelling strategy. This is particularly true for type 2 diabetes, which is clearly linked to modifiable risk factors (e.g., obesity and a sedentary lifestyle). The Diabetes Prevention Program (DPP) demonstrated that intensified lifestyle or drug intervention in individuals with IGT prevented or delayed the onset of type 2 diabetes. Cost-effective strategies for promoting lifestyle modification in high risk individuals, outside the setting of a controlled, clinical trial, need to be established. Population-based, as well as generalizable, clinic-based, strategies are needed to establish cost-effective programs to (1) identify individuals at high risk who could benefit from prevention programs; and/or (2) successfully promote lifestyle change.

Childhood obesity, the prevalence of which has more than doubled in the past two decades, is a major risk factor for type 2 diabetes. Indeed, the increase in childhood obesity has been linked to an alarming rise in type 2 diabetes in the pediatric population. Family-based behavioral interventions have been shown to have a long-term impact on degree of overweight; however, cost-effective interventions in primary care and community-based settings are needed. In addition, while behavioral treatment of obesity in adults leads to clinically significant weight loss, prevention of weight regain remains an elusive goal for many. Continuing care models show promise in promoting long-term weight maintenance, and cost-effective means of providing such care need to be developed.

Research Goals and Scope

The objective of this PA is to support research to develop and test (1) improved methods of health care delivery to patients with or at risk of diabetes; (2) improved methods of diabetes self management; and (3) cost effective community-based strategies to promote healthy lifestyles that will reduce the risk of diabetes and obesity. Studies can target the health care system, the provider and/or the patient. Generally, these studies will take interventions that have been demonstrated to be beneficial by controlled laboratory or clinical investigations (e.g., intensive glycemic control, increased physical activity in individuals at risk for diabetes), and extend or adapt these interventions to larger populations or other settings. Of particular interest are studies targeting underserved and minority populations.

ANDROGEN RECEPTOR IN PROSTATE GROWTH AND CANCER
(RFA DK-02-031) http://grants1.nih.gov/grants/guide/rfa-files/RFA-DK-02-031.html

FY 2003 Action
This RFA seeks applications that will foster greater understanding of the role of the androgen receptor (AR) in carrying out the signaling program that reflects androgen action in the prostate gland. The long-term goal is to provide a better understanding of the role of androgens, and the AR, in growth and development of the prostate, and/or development and progression of prostate cancer.

Background
Advances in the nuclear hormone receptor (NR) superfamily, of which the androgen receptor is a member, have revealed a complex pattern of hormone action in target tissues and cells in response to hormone (ligand). NRs are ligand-dependent and -independent transcription factors, with roles in development, reproduction, metabolism, and disease. For many of the known NRs, including the steroid receptor subfamily (ER, PR, GR, and AR), evidence now points to formation of large, multicomponent complexes in the nucleus, at the promoter/enhancer region of target genes, to effect regulation of expression. The complexes may include coactivators (SRC-1, -2, -3), corepressors (NCoR, SMRT), RNA transcripts (SRA), histone acetylases (HAT), or deacetylases (HDAC), methylases (CARM1), components of the RNA polymerase machinery, and chromatin remodeling factors (ACTR). Various combinatorial groupings of these factors appear to be essential for expression of genes in a regulated and specific manner. Importantly, some factors when present at inappropriate levels have been implicated in malignant transformation, including overexpression of the SRC-2 family member AIB(amplified in breast cancer)1 coactivator in some tumors of breast, and the fusion protein ETO (eight:to:twentyone), a hematopoietic transcription factor fused to a NR (RAR) creating an aberrant transcription factor that recruits high levels of corepressor in some leukemias. Exciting use of this basic knowledge has led to development of an RAR ligand that relieves repression and leads to differentiation of the tumor cells, resulting in remission. In these examples alterations in the combinatorial complex subverts the normal program of regulation leading or contributing to tumor formation.

Research Goals and Scope
The specific objectives of this research solicitation include, but are not limited to: (1) regulation of gene expression in prostate in response to androgens; (2) modulation of the androgen signaling program by other signals (cross-talk) and potential role in growth and tumorigenesis; (3) determination of the components of AR-nuclear accessory protein complexes responsible for determination of specificity and regulation of gene expression; (4) role of aberrant signaling in tumor progression and possible role(s) in development of androgen-independent tumor growth; (5) identification of AR target genes up- and/or down-regulated by hormone in normal and transformed prostate through use of DNA arrays, high throughput proteomics, *in silico* computational, or other means; (6) development of systems to identify and/or utilize model androgen-sensitive genes for studies into the mechanism of action of the AR; (7) determination of key AR-cofactor interaction sites as potential targets for development of therapeutic intervention; and (8) elucidation of the mechanism(s) of action of selective receptor modulators (SRMs) with potential AR antagonist or selective partial agonist activity.

PROTEOMICS IN DIABETES AND OTHER ENDOCRINE AND METABOLIC DISEASES

FY 2003 Action

This initiative seeks to promote the use of proteomic technologies for studying diabetes, and other endocrine and metabolic diseases. A multiphase process is envisioned with an initial program announcement followed by a conference in 2003 to stimulate collaboration between laboratories developing proteomic technologies and clinical and basic researchers in the areas of diabetes, endocrinology and metabolic diseases.

Background

High throughput DNA sequencing has changed biomedical research. The complete sequence of the genome for 92 organisms and the nearly complete sequence of many others, including the human, are giving a new vision to the study of biological systems. It is, however, apparent that knowledge of the genome alone is not sufficient for a complete understanding of complex biological processes. While the genome is the same in different cell types within an organism and does not change with time, the proteome varies with time and is different in different cell types. It should however be noted that the function is usually fulfilled from the proteins containing the actual information rather than the potential as indicated by the gene.

In view of recent large-scale data showing that often the correlation between mRNA quantities and protein quantities is poor, we cannot limit our studies at the mRNA or gene level and we ought to investigate biological problems also at the protein level. To further emphasize the importance of studying the proteome it should be mentioned that post-translational modifications, regulation of protein function by proteolysis, and composition of macromolecular complexes could only be determined at the protein level.

Recent developments in proteomics indicate that the technology available is already sufficiently advanced to approach many relevant biological questions. Some of these technologies include: (1) two-dimensional gel electrophoresis for profiling complex mixtures coupled to mass spectrometry or other methods for protein identification; (2) isotopically labeled reagents for the comparison of two different biological states (e.g., disease versus control) using mass spectrometry; (3) protein or antibody arrays; (4) yeast two-hybrid system, phage display or immunoprecipitation coupled to mass spectrometry for studying protein-protein interactions; (5) characterization of macromolecular complexes using antibodies, DNA, RNA, or other molecules as a bait followed by mass spectrometry identification; and (6) computational methods for structure/function prediction.

None of the above technologies is capable of analyzing the whole proteome at once but, the study of a subset of the proteome is already feasible, and their use properly applied to specific biological questions would give new insights about the system or the disease under study. It should also be noted that there is an apparent need to improve the present technologies and develop novel approaches for studying the proteome, thus this initiative will also encourage technology development. However, these developments would be of particular interest when aimed to solve problems or to understand diseases of interest to NIDDK.

Research Goals and Scope

Examples of projects that this initiative intends to encourage include: (1) identification of surrogate markers for the plasma proteome at different stages of diabetes and comparing the plasma proteome of diabetic and pre-diabetic *versus* control subjects; (2) characterization of animal and cell models relevant to diabetes and other endocrine and metabolic diseases using proteomic approaches; (3) analysis of the signal transduction network of the insulin receptor and other receptors relevant to the Institute's mission using proteomic approaches; (4) identification of novel signaling molecules and pathways involved in cell development, differentiation, transcription, and functions as they apply to diabetes, endocrinology, and metabolic diseases; (5) use of proteomic approaches for studying the regulation of hormones, carbohydrate metabolism, nuclear receptors (e.g. adrenal glucocorticoids, mineralocorticoids, estrogen, progesterone, and androgen receptors), surface receptors (e.g., G-protein coupled receptors, Ser/Thr kinase receptors, growth factor receptors, and cytokine receptors) and their action; (6) development and/or use of computational proteomics tools to analyze and/or annotate the genome as it might apply to information relevant to diabetes, endocrinology, or metabolic diseases; (7) identification of novel drug targets or novel drugs using proteomic approaches that might be relevant to diabetes, endocrinology, or metabolic diseases; and (8) characterization of subsets of the proteome for studying the effect of drugs relevant to diabetes and other endocrine or metabolic diseases.

THE LIFE CYCLE OF THE ADIPOCYTE

FY 2003 Action

An RFA will be issued to encourage applicants to develop the necessary biological procedures, reagents, and tools to study fundamental aspects of the life cycle of the adipocyte, with particular emphasis on adipose tissue turnover and remodeling.

Background

The adipocyte is a key cell in the development of many metabolic diseases including diabetes, obesity, and both familial and acquired lipodystrophy. Given that peripheral and visceral adipose tissues are accessible to biopsy, fat tissue is a reasonable target for animal and human studies. Recent advancements in our understanding of stem cell and progenitor cell biology, and the development of methods for whole genome and proteome analyses allow new approaches to be applied to the study of the adipocyte life cycle.

The congressionally-established Diabetes Research Working Group (DRWG) report "Conquering Diabetes, A Strategic Plan for the 21st Century" and an international workshop, entitled "Lipoatrophic Diabetes and Other Syndromes of Lipodystrophy," emphasized the importance of understanding more about the life cycle of insulin responsive tissues (e.g., liver, skeletal muscle, and fat) in healthy individuals, understanding the cross-talk among these tissues, and elucidating how the life cycle of these tissues are altered in metabolic diseases such as diabetes and obesity, which are affecting an ever growing number of people. Furthermore, with the widespread use of highly active antiretroviral therapy (HAART) for the treatment of HIV disease, patients are now living longer. Although the overall health of HIV-infected individuals is improving, concerns are now arising that HAART therapies may be associated with adverse metabolic effects, such as hyperlipidemia, insulin resistance, and changes in body composition. Studies are needed to elucidate the mechanism underlying these various HIV-associated lipodystrophies and their connection with antiretroviral therapies.

Research Goals and Scope

The NIDDK intends to support multidisciplinary, investigator-initiated projects that explore fundamental aspects of the life cycle of the adipocyte. This initiative encourages investigators to develop the necessary biological procedures and reagents for characterization of adipocyte progenitor cells at multiple stages of determination and commitment into the adipocyte lineage, for use in identifying fat cell commitment factors, and to use in the study of adipose tissue turnover and remodeling. Use of genomic and proteomic methods, as well as other advanced tools and technologies to study the normal and disease-related turnover and remodeling of adult adipocytes from various fat depots; to determine how fat tissues are maintained during adult life; and to investigate how adipocytes are affected by age, environmental factors, drug treatment, and metabolic diseases are also encouraged. The ultimate goal is to use this increased understanding of the life cycle of the adipocyte to develop novel treatments for metabolic diseases including type 2 diabetes, obesity, familial lipodystrophy, and acquired lipodystrophy associated with HIV infection and treatment.

DEVELOPMENT OF THE ENDOCRINE PANCREAS (PA-02-152)

FY 2003 Action

This program announcement is intended to stimulate the application of advances in developmental biology, specifically in developmental genetics, embryology, and stem cell biology, to study pancreatic development. Collaborative efforts that link expertise in basic developmental biology or stem cell biology and diabetes are strongly encouraged. It is anticipated that this research will ultimately lead to a better understanding of the pathways required for the development and regeneration of the endocrine pancreas, both *in vivo* and *in vitro*. The NIH will allow federal funding for research using human embryonic stem cells and an NIH registry for human embryonic stem cell lines has been established (http://escr.nih.gov/). This PA will support efforts in the characterization of these human embryonic cell lines, as well as human fetal and adult stem cells as they relate to the specification of endoderm and differentiation of pancreatic islet cell types. This PA is intended to intensify investigator-initiated research, to attract new investigators to the field, and to encourage interdisciplinary approaches to research in this area.

Background

Processes fundamental to the development of all organ systems include germ layer specification, cell fate determination, pattern formation, proliferation, and differentiation. Inductive signals, including those of the TGF beta family and FGF family, are produced by the notochord, the tissue adjacent to the endoderm, and are thought to be responsible for specifying endoderm. These signals induce downstream endodermal-specific transcriptional factors such as the Mix-type homeobox proteins, Gata factors, and Sox proteins. During embryogenesis, endoderm-derived organ formation is accomplished through an orchestration of signaling pathways that specify the distinct organ anlagen. Signals such as sonic hedgehog must be excluded from the developing pancreatic anlagen for proper pancreas development, while signals produced by the mesenchyme are necessary for pancreatic differentiation into specified cell types. Development of endocrine organs involves the "budding morphogenesis" of an epithelial layer in order to create a specific organ. Additionally, developmental signals that arise from blood vessels can regulate pancreatic organogenesis. Some factors, such as *Hex,* do not influence specific cell type decisions but may control competence. Initiation of bud formation requires the transcriptional factor *HlxB9* while the *pdx1/IDX1* is necessary for pancreas development and outgrowth. Genes of the Notch/Delta pathway regulate the ability of a cell to initiate differentiation in the endocrine pancreas. For example, *ngn3,* a key component of the Notch pathway is required for the formation of the endocrine pancreas. Cell fate decisions in the endocrine pancreas involve a host of transcriptional regulators which include *Pax4*, *Nkx2.2*, *Nkx 6.1*, *Pax6*, *Isl1* and *NeuroD*. For the endocrine pancreas, this ultimately means differentiation into the cell types responsible for production of insulin, glucagon, etc., TGF alpha/betas and hedgehog signaling pathways, in their regulation of the extracellular matrix, may be key activators in islet morphogenesis. Little is known about the mechanisms that regulate the migration of islet precursors, but it is likely that cell adhesion molecules such as integrins and perhaps some of the molecules involved in cell guidance in the nervous system could play a role.

In the last decade, studies in non-vertebrate genetic models of *C. elegans* and *Drosophila* have provided a wealth of scientific advances in the definition of early developmental pathways. In

the next decade, the emerging genetic model, zebrafish, can be exploited for dissecting events in endoderm development and morphogenesis of the pancreas. Non-genetic models such as *Xenopus* and chick have proven useful in identifying and characterizing novel signals and associated components of signaling pathways as well as transcriptional regulators in endoderm development and organ morphogenesis. Understanding the regulation of cell- and tissue-specific gene expression in pancreatic development has lead to the generation of useful transgenic mouse models of diabetes. These and future mouse models will be useful for determining pancreatic cell lineage and for prospectively isolating and characterizing stem/progenitor cells from the pancreas. Public databases such http://www.cbil.upenn.edu/EPConDB/ focused on the developing endocrine pancreas will serve as a resource in identifying novel genes that play a role in pancreas development and in identifying potential cell-specific surface markers at different stages of pancreatic development. Furthermore, the use of cDNA microarrays enriched in genes expressed in the developing endocrine pancreas will aid in the characterization of pancreatic stem/progenitor cells by establishing gene expression profiles and also aid in the phenotypic characterization of the growing number of mouse models of diabetes. In the future, related resources will be available through the NIDDK-funded Beta Cell Biology Consortium (http://www.betacell.org).

Type 1 and type 2 diabetes result from the loss or dysfunction of insulin-producing cells of the pancreas. Replacement of these cells, through transplantation, could offer lifelong treatment for diabetics. However, a major problem in implementing treatment is the lack of sufficient islet cell tissue for transplantation. Embryonic stem cells and other tissue-specific stem cells could potentially provide a limitless source of islet cells for transplantation therapies. Experimentation on mouse and human embryonic stem cells has shown that, in principle, these cells are capable of giving rise to pancreatic islet-like structures that produce insulin under certain culture conditions. Putative stem/progenitor cells have been isolated from human pancreatic duct and islet tissue, however further characterization of these cell populations is needed. These studies are still in their infancy, and a more fundamental understanding of how to efficiently generate large numbers of functioning pancreatic islets from embryonic or tissue-specific stem cells remains a challenge.

Research Goals and Scope

- Developmental genetic screens for identifying mutations that affect pancreas development.
- Identification of signals, signaling pathway components and transcriptional factors that regulate endoderm specification, dorsal pancreatic bud formation, and pancreatic fate determination.
- Role of cell-cell interactions, differential cell adhesion, and cell motility in morphogenesis of the pancreatic islet.
- Role of extracellular matrix in islet cell morphogenesis.
- Molecular markers for defining all stages of pancreatic development, including cell-specific markers of stem/progenitor cells of the endocrine pancreas.
- Studies examining endocrine pancreatic cell lineage, including alpha, beta, and delta cell fate determination and differentiation.
- Molecular characterization and comparison of human embryonic stem cell lines and other human tissue-specific stem/progenitor cells to produce endoderm and ultimately differentiated cells of the endocrine pancreas.

- Prospective isolation, purification and characterization of pancreatic stem/progenitor cells.
- Development of clonogenic assays, both *in vitro* and *in vivo*, for characterizing stem/progenitor cells of the pancreas.
- Identification of growth conditions required to generate differentiated cells of the endocrine pancreas from mammalian stem/progenitor cells.
- Use of model systems for the study of regeneration of the endocrine pancreas.
- Studies to understand the molecular basis of transdifferentiation of gut, liver, and exocrine pancreatic stem/progenitor cells to produce pancreatic islets.
- Studies examining the plasticity of hematopoietic, mesenchymal, liver, neural and other tissue-specific stem/progenitor cells in the formation of pancreatic islets.

COMPLEX FORMATION IN HORMONAL REGULATION OF GENE EXPRESSION (PA-02-100) http://grants1.nih.gov/grants/guide/pa-files/PA-02-100.html

FY 2003 Action

This initiative represents a re-issue of PA-99-111 (Co-Activators and Co-Repressors in Gene Expression). The original PA was based on an NIDDK Workshop ("Co-Activators and Co-Repressors in Gene Expression" held December 15-16, 1998) and was designed to stimulate research to address the fundamental underlying mechanisms by which nuclear accessory proteins, such as co-activators and co-repressors, mediate signaling through hormone receptors at the level of the regulation of gene expression. The re-issued PA seeks to exploit and expand upon advances made since then in this, and other related areas and refine the role of higher order complex formation in effecting hormonal regulation of gene expression.

Background

Regulation of hormone action involves both short- and long-term functions expressed in minutes-to-hours as either rapid changes in cellular metabolism or change in gene expression. At the level of gene expression numerous cytoplasmic and nuclear accessory proteins have been implicated in mediating hormone action. Co-repressors and co-activators are important examples that represent classes of nuclear accessory proteins that also include elements of the basal and regulated transcription machinery in cells. Formation of higher order complexes with nuclear accessory proteins and hormonal signaling complexes is an important part of the process of activation of gene expression. An earlier NIDDK workshop entitled "Co-Activators and Co-Repressors in Gene Expression" (December 15-16, 1998) highlighted the importance of emerging information on the roles of nuclear accessory factors in the regulation of signaling at the level of transcription. Their ultimate role is in mediating the action of transcription factors, representing hormone receptors or the end effectors of hormone receptors, in enhancing or suppressing the expression of specific genes. Thus, combinatorial complexes that form, dissolve, and re-form, at the regulatory segments of target genes contribute to specificity and overall regulation with altered levels of expression, mutation or post-translational modification of constituent components also contributing to disease development and/or progression. As a consequence, these factors have also now become targets for therapeutic intervention.

Research Goals and Scope

The specific objectives of this research solicitation include: (1) role of co-activators/co-repressors in the regulation of tissue-specific gene expression; (2) role of cytoplasmic factors in hormone or receptor processing and/or signal propagation to the nucleus; (3) identification of model systems that allow for study *in vitro* or *in vivo* of gene expression; (4) role(s) of nuclear accessory proteins in regulation of nuclear hormone action in target cells; (5) novel factor(s) associated with hormone action involved in disease genesis, including breast and prostate cancer, obesity, insulin resistance, diabetes, and osteoporosis; (6) Selective Receptor Modulators (SRM) with potential effects on disease development and/or progression; (7) structural biology of receptor/interacting protein and/or cofactor interaction focusing on interactions with other receptor interacting proteins, co-activators or co-repressors, the ligand, or hormone response elements (HREs) in signal propagation; (8) role(s) of chaperone proteins in regulating receptor function and/or interaction with ligands or nuclear accessory proteins, including nuclear localization and/or proteasomal degradation; (9) signaling cross-talk between classes of receptors

and cytoplasmic and/or nuclear accessory proteins and effects on regulation of gene expression and disease initiation/progression; and (10) molecular mechanisms by which breast and prostate tumors acquire hormone-independence.

BONE ANABOLIC HORMONES, THEIR RECEPTORS AND SIGNAL TRANSDUCTION PATHWAYS

FY 2003 Action

The objective of this initiative is to elicit grant applications that focus on systemic hormones, local growth factors and bone-active cytokines with bone anabolic effects. The signal transduction pathways recruited by the receptors of these hormones and growth factors is of particular interest. Although the primary focus is on basic research, the long-term objective is to identify potential targets of therapeutic value in the treatment of diseases that adversely affect bone including, but not limited to, osteoporosis due to loss of sex steroids, use of immunosuppressive drugs, and hyperparathyroidism.

Background

Bone biology has benefited over the last decade from a tremendous explosion of information derived from analyses of mutations affecting skeletal development in man and mouse. Indeed, studies on bone development have revealed roles for signaling through peptides of the PTHrP, hedgehog, Wnt, FGF, and BMP/TGF-beta family members; transcription factors from the Hox, Pax, Forkhead, NFkB, AP-1, Runx2/Cbfa1, and Osx families; and signal transducing molecules such as tyrosine kinases (e.g. c-src, c-fms), serine / threonine kinases, TRAFs and MAP kinases in bone cell fate determination, differentiation, and formation of mature bone. However, it is clear that diseases that affect bone, such as osteoporosis and primary hyperparathyroidism, result in gradual loss of bone leading to osteopenia, which is a leading cause of fractures in adults. Hormones are key regulators of bone mass and osteopenia may result from alterations in hormone action, such as loss of estrogen production in post-menopausal women or of androgens in older men, excessive production of parathyroid hormone (PTH) as in primary hyperparathyroidism, or glucocorticoid excess as a consequence of chronic steroid use in immunosuppressive therapy. Other imbalances in local growth factors and/or bone-active cytokines resulting from a variety of conditions (e.g., chronic inflammation, rheumatoid arthritis) may also contribute to osteopenia.

Research supported by previous Program Announcements (PA-96-076 and PA-00-017) and other initiatives revealed that growth factor signaling in developing and mature bone cells is key to maintaining proper mineral balance and peak bone mass. Recent data from a large clinical trial on the use of estrogen plus progestin in postmenopausal women demonstrated that the beneficial effects on bone are by its adverse effects on other organs (JAMA 288:321). A second study concluded that women using estrogen (alone) replacement therapy were at increased risk of developing ovarian cancer (JAMA 288:334). The development and use of Selective Estrogen Receptor Modulators (SERMs) has served to partially offset these side effects while giving some degree of protection against post-menopausal bone loss. It is critical to understand the mechanism underlying the beneficial effects of estrogen on bone in order to target new therapeutic agents that promote bone growth and integrity. In addition, other therapeutic agents have been developed that alter mineral content and/or molecular structure of bone (e.g., bisphosphonates), or that alter hormonal balances (e.g., calcitonin, vitamin D). The first truly bone anabolic therapeutic agent, intermittently administered PTH, will likely enter the market in the near future; although, the mechanism of PTH action in this context remains to be determined.

Research Goals and Scope

The major areas of interest and potential that have been identified relevant to this program announcement are:

- The mechanism(s) of action of sex steroids, including estrogen, selective estrogen receptor modulators (SERMs), partial agonists, and agents with estrogen-like activity in bone; androgens and androgen-like agents (SARMs) which express positive, anabolic effects on bone; other members of the nuclear hormone receptor superfamily, including PPAR, vitamin D, and others and their role(s) in signaling in bone cells and bone cell precursors.
- PTH and/or PTHrP, and agonists that express PTH- or PTHrP-like anabolic effects in bone and the mechanisms of signaling in developing and mature bone.
- LRP5, its interactions with Dickkopf-1 and the Wnt signaling pathways.
- Insulin-like growth factor I (IGF-I), its receptors and binding proteins, or any other component of the IGF axis that signal in bone.
- Fibroblast growth factor(s) and their role(s) in bone/cartilage development and/or angiogenesis related to bone.
- Members of the TGF/BMP family, their receptors and signal transducers such as members of the SMAD family.
- Bone active cytokines including but not limited to Colony Stimulating Factors (e.g. CSF-1), RANKL/RANK/OPG axis, and cytokine products of Th-1 and Th-2 T cells (e.g., interferons, TNFs, interleukins) which can modulate bone homeostasis, their receptors, and signaling pathways.
- Role of novel transcription factors, such as Osx, Runx2/Cfba1, hox gene products, and their mechanisms of signaling in bone cells and their precursors.

This is by no means a complete listing of potentially important hormones, growth factors, or cytokines. The general focus should be on developing an understanding of the putative mechanism(s) of action of these agents with the goal of defining what aspect(s) of signaling in bone may be affected and how anabolic or other beneficial therapeutic actions may be achieved and sustained. Support for investigator initiated clinical trials designed to test the efficacy of novel anabolic factors or novel therapy regimens of clinically proven compounds may be sought through this initiative.

DIVISION OF DIABETES, ENDOCRINOLOGY AND METABOLIC DISEASES
Conferences and Workshops

Beta Cell Biology Consortium Investigator's Retreat: Pancreatic Development and Stem Cells
Date: November 21-23, 2002
The agenda includes talks and poster presentations which are focused on stem/progenitor cells, islet cell differentiation, formation, and function, and islet engineering/transplantation. Break-out discussions on animal models, stem cells, gene expression profiling, and bioinformatics are planned.

Workshop on Proteomics in Diabetes and Other Endocrine and Metabolic Diseases
Date: April 23-25, 2003
The purposes of this workshop are to entice applications using proteomics to study diabetes and stimulate collaboration between laboratories developing proteomic technologies and clinical and basic researchers in the areas of diabetes.

Career Development Awardees (K Award) Conference
Date: Spring 2003
This conference is a two-day workshop for NIDDK-funded K awardees to learn more about the organization of the NIH, the role of the NIH staff, grant writing skills, the peer review process, negotiating for a new position and a start-up package, and other issues related to career development.

Microvascular Complications of Diabetes: 20 Years after Initiation of DCCT
Date: Spring 2003
The aim of this symposium is to discuss the mechanisms by which intensive glycemic treatment in the DCCT/EDIC persists in reducing the onset and progression of retinopathy, nephropathy, and neuropathy. Attendees are expected to discuss the role of endothelial biology, blood pressure, lipids, immune factors, growth factors, and genetic factors as they impact on microvascular complications, and further studies in EDIC that may help our understanding of the pathogenesis.